

# Progress in the Synthesis of Oxindole–Lawsonone Molecular Hybrid Scaffolds: A Review

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**Abstract:** Oxindole and 1,4-Naphthoquinone both are the versatile heterocyclic scaffolds which not only found in many naturally occurring and pharmaceutically imperative compounds but also have explored as an important precursor in the synthesis of a library of structurally diverse molecular frameworks desirable for biological studies. For a few decades, significant emphasis is given on the synthesis of both of these important privileged scaffolds to accomplish promising new heterocycles with chemical and biomedical relevance. Due to such prevalence and prominence of oxindole and 1,4-naphthoquinone frameworks in medicinal and synthetic chemistry, many researchers have taken efforts to synthesize the oxindole-naphthoquinone molecular hybrid in a single nucleolus. These efforts have led to the development of different approaches and green technologies in recent years, which includes nano catalysts, microwaves and, ultrasound irradiation. In this review, we have focused our attention, specifically, to provide insight into the modern approaches to the synthesis of oxindole-1,4-naphthoquinone molecular hybrid. The review is mainly made up of four main parts which contain 2-component, 3-component, 4-component, and other multistep miscellaneous approaches utilized to synthesize this oxindole-1,4-naphthoquinone molecular hybrid. These four main parts are also subdivided according to different substituents present on oxindole-1,4-naphthoquinone molecular hybrid. This review focused specifically on the collection of literature on the reaction of isatin with 2-hydroxyl-1,4-naphthoquinone(Lawsonone) to afford oxindole-1,4-naphthoquinone molecular hybrid.

**Keywords:** Molecular hybridization, Oxindole, Lawsonone, Multicomponent reaction, Sonochemistry, Green synthesis

## I. INTRODUCTION

In synthetic and medicinal chemistry, the concept of ‘Molecular hybridization’ is utilized to a large extent which involves the formation of structural hybrid scaffolds by the combination of different molecules. The main objective of molecular hybridization is to join different bioactive molecules to produce a hybrid compound with improved activity. These Hybrid Molecular scaffolds are dual-acting multi-functional compounds which are also known by different terms like multi-target directed compounds, me-better drugs, multiple ligand molecules, double drugs, combinational drugs, dual–drugs multiple-drugs, bifunctional drugs, bivalent ligands, drugs with two heads, etc. Synthesis of such hybrid molecular scaffolds is achieved by linking Pharmacophores subunits directly or indirectly using linkers or spacers.

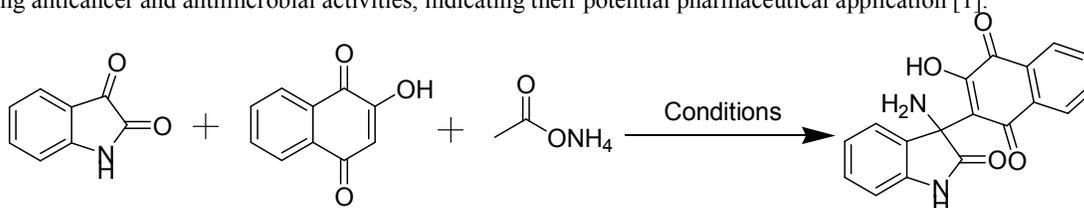
Nowadays joining different Pharmacophores subunits to afford hybrid molecular scaffolds, is an emerging strategy used frequently in the process of designing and discovery of new drugs. In this review, we have focused our attention specifically on the molecular hybrid consisting of oxindole and lawsonone framework, because these two frameworks are cogent heterocyclic scaffolds which not only found in various natural and pharmaceutically important compounds possessing several biological activities but also explored as a versatile starting material decisively used in the synthesis of various organic compounds.

Oxindole which is also known as the derivative of Isatin is an important class of heterocyclic compounds that emerged as an interesting pharmacophore possessing diverse biological activities. Furthermore, the chiral 3,3-disubstituted oxindole is a privileged framework found in various natural products and pharmaceutically active compounds.



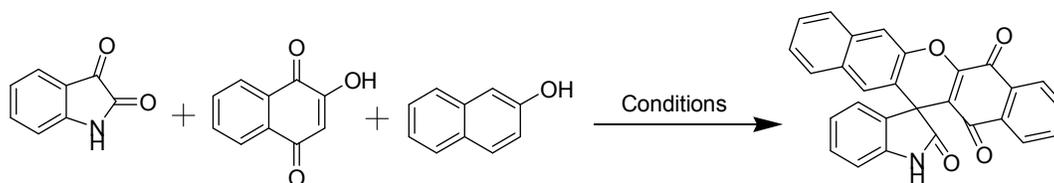
As a class of important 3,3-disubstituted oxindoles, 3-substituted 3-hydroxyindolin-2-ones have attracted considerable attention because of their diverse biological activities. During recent years, several review articles were published on a synthesis of 3-hydroxy-2-oxindoles and spiro-fused cyclic frameworks using isatin or oxindoles. The Friedel–Crafts reaction, Aldol reaction, Michael reaction, Morita Baylis–Hillman reaction, Grignard reaction, and Henry reaction have been used commonly for the effective synthesis of 3-substituted-3-hydroxy oxindole derivatives. With the advancement in the field of catalysis, a large number of other methods for the synthesis of a diverse range of substituted oxindoles have been developed.

Che et al. reported the three-component reaction of isatin, 2-hydroxyl-1,4-naphthoquinone (Lawson), and ammonium acetate to form 2-(3-amino-2-oxindolin-3-yl)-3-hydroxynaphthalene-1,4-dione derivatives (**scheme 1**) are reported under catalyst-free condition using ethanol at reflux temperature a catalyst-free one-pot three-component reaction involving isatin, lawson, and amines to generate oxindole–lawson hybrids. The process was mild, efficient, and yielded diverse substituted derivatives. NMR and mass spectrometry confirmed structures. These compounds exhibited strong anticancer and antimicrobial activities, indicating their potential pharmaceutical application [1].



**Scheme 1:** Synthesis of 2-(3-amino-2-oxindolin-3-yl)-3-hydroxynaphthalene-1,4-dione derivatives

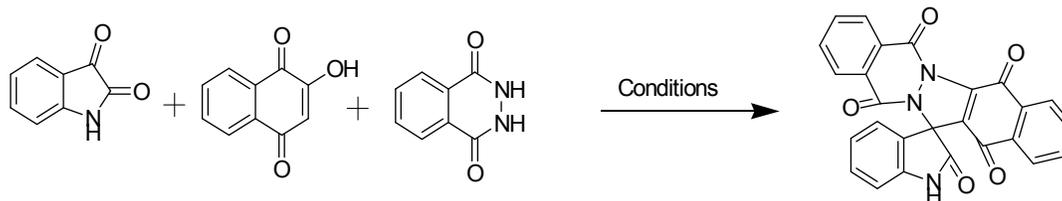
Reaction of isatin, 2-hydroxyl-1,4-naphthoquinone (Lawson) and 2-Naphthol to form spiro-[dibenzo[a,i] anthenes-14,3'-indoline]-2',8,13-triones derivatives (**Scheme 2**) have reported by Yang et al. Cellulose sulfate, ionic liquid [Hmim][HSO<sub>4</sub>] and H<sub>4</sub>SiW<sub>12</sub>O<sub>40</sub> have been explored as a catalyst in this reaction. Used H<sub>4</sub>SiW<sub>12</sub>O<sub>40</sub> as a green catalyst for spirooxindole synthesis via condensation of isatin and diketones. The catalyst enhanced reaction rate, yield, and selectivity. Structural analysis was done using NMR and mass spectrometry. The products demonstrated antimicrobial and cytotoxic activities, highlighting their medicinal relevance [2].



**Scheme 2:** Synthesis of spiro-[dibenzo[a,i] anthenes-14,3'-indoline]-2',8,13-triones derivatives.

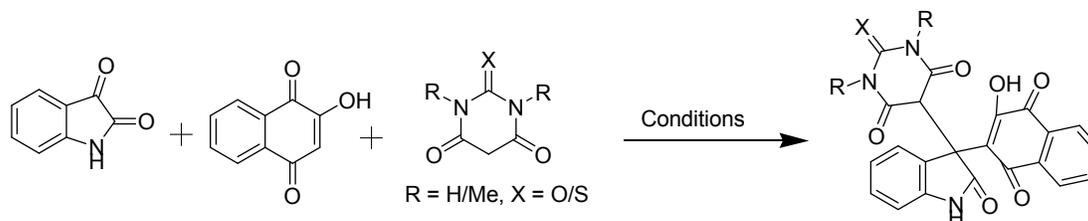
Vajargahy et al. Vajargahy, Milad Pedarpouret al reported three-component reaction of isatin, 2-hydroxyl-1,4-naphthoquinone (Lawson), and 2,3-dihydrophthalazine-1,4-dione to form spiroindazolophthalazine derivatives using H<sub>2</sub>SO<sub>4</sub> as a catalyst in H<sub>2</sub>O:EtOH solvent system under Ultrasound condition (**Scheme 3**). The products were characterized using standard spectroscopic techniques. The derivatives showed promising antibacterial and anticancer activities, highlighting their potential as therapeutic agents and demonstrating the advantages of sonochemical green synthesis [3].





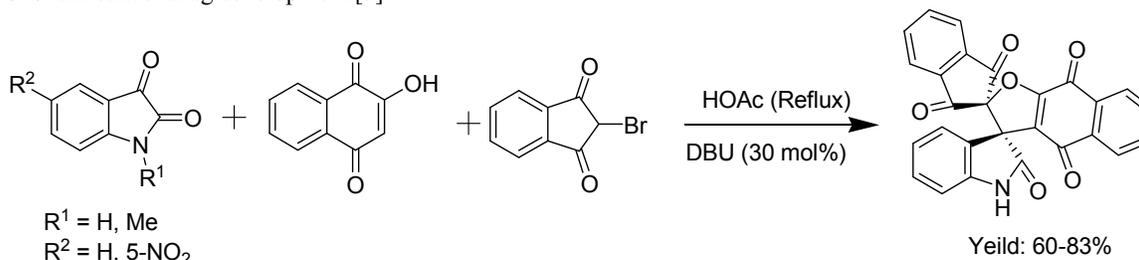
**Scheme 3:** Synthesis of spiroindazolophthalazine derivatives

Brahmachari *et al.* synthesized the three-component reaction of isatin, 2-hydroxy-1,4-naphthoquinone (Lawson), and Barbituric acids to form substituted 1,4-Naphthoquinonyl-2-oxoindolinylpyrimidines derivatives (**Scheme 4**). Isatin derivatives, lawson, and pyrimidine-forming agents underwent condensation and cyclization to yield hybrid scaffolds. The approach was environmentally benign and gave high yields. Biological evaluation revealed potential anticancer and antimicrobial activities. These compounds serve as scaffolds for drug discovery and medicinal chemistry research [4].



**Scheme 4:** Synthesis of 1,4-Naphthoquinonyl-2-oxoindolinylpyrimidines derivatives

Ahadi, Somayeh *et al.* reported, the new three-component reaction of isatin, 2-hydroxy-1,4-naphthoquinone (Lawson), and 2-bromo-2H-indene-1,3-dione to form a new Bisspirooxindole (**Scheme 5**). framework containing vicinal spirocenters by employing DBU as a catalyst in acetic acid. The reaction involved isatin derivatives and diketones under mild conditions, allowing stereoselective formation of complex spiro frameworks. The products were analyzed using NMR, IR, and mass spectrometry. These hybrids exhibited cytotoxic and antimicrobial properties, providing a basis for anticancer drug development [5].



**(Scheme 5):** Synthesis of Bisspirooxindole

## II. METHODOLOGY

The three-component reaction of isatin, 2-hydroxy-1,4-naphthoquinone (Lawson), and ammonium acetate to form 2-(3-amino-2-oxoindolin-3-yl)-3-hydroxynaphthalene-1,4-dione derivatives are reported under catalyst-free condition using ethanol at reflux temperature (Scheme 1). Summary of reaction conditions for the synthesis of 2-(3-amino-2-oxoindolin-3-yl)-3-hydroxynaphthalene-1,4-dione derivatives are shown in **Table 2.1**.



**Table 2.1:** Reaction conditions for the synthesis of 2-(3-amino-2-oxoindolin-3-yl)-3-hydroxynaphthalene-1,4-dione derivatives

Entry	Conditions				
	Catalyst	Solvent	Time	Temp.	Yield
1.	Catalyst-free	EtOH	2 h	78°C	99%
2.	Catalyst-free	EtOH	2 h	78°C	98%

Reaction of isatin, 2-hydroxyl-1,4-naphthoquinone(Lawsone) and 2-Naphthol to form spiro-[dibenzo[a,i] anthenes-14,3'-indoline]-2',8,13-triones derivatives have reported by various groups. (Scheme 2). Cellulose sulfate, ionic liquid [Hmim][HSO<sub>4</sub>] and H<sub>4</sub>SiW<sub>12</sub>O<sub>40</sub> have been explored as a catalyst in this reaction. Table 2.2 shows the summary of reaction conditions for the synthesis of spiro-[dibenzo[a,i] anthenes-14,3'-indoline]-2',8,13-triones derivatives reported by various researchers.

**Table 2.2:** Reaction conditions for the synthesis of spiro-[dibenzo[a,i] anthenes-14,3'-indoline]-2',8,13-triones derivatives

Entry	Conditions				
	Catalyst	Solvent	Time	Temp.	Yield
1.	Cellulose sulfate	Solvent –free	50 min	100°C	96%
2.	[Hmim][HSO <sub>4</sub> ], pH 1	Solvent –free	1.5 h	100°C	91%
3.	H <sub>4</sub> SiW <sub>12</sub> O <sub>40</sub>	Solvent –free	1h	110°C	89%

Vajargahy, MiladPedarpouret *al* reported three-component reaction of isatin, 2-hydroxyl-1,4-naphthoquinone (Lawsone), and 2,3-dihydrophthalazine-1,4-dione to form spiroindazolophthalazine derivatives using H<sub>2</sub>SO<sub>4</sub> as a catalyst in H<sub>2</sub>O:EtOH solvent system under Ultrasound condition (Scheme 3). The reaction condition of this reaction is shown in Table 2.3.

**Table 2.3:**Reaction conditions piroindazolo phthalazine derivatives

Condition					
Catalyst	Solvent	Time	Temp.	Yield	
H <sub>2</sub> SO <sub>4</sub> (Ultrasound)	H <sub>2</sub> O: EtOH	3 h	60°C	73%	

The three-component reaction of isatin, 2-hydroxyl-1,4-naphthoquinone (Lawsone), and Barbituric acids to form substituted 1,4-Naphthoquinonyl-2-oxoindolinylpyrimidines derivatives is reported by two different research groups (Scheme4). H<sub>2</sub>NSO<sub>3</sub>H and *p*-toluenesulfonic acid are the two different catalysts explored in this synthesis. Table 2.4 highlights the reaction conditions for the synthesis of substituted 1,4-Naphthoquinonyl-2-oxoindolinylpyrimidines derivatives.

**Table 2.4:** Reaction conditions for the synthesis of substituted 1,4-Naphthoquinonyl-2-oxoindolinylpyrimidines derivatives.

Entry	Condition				
	Catalyst	Solvent	Time	Temp.	Yield
1.	H <sub>2</sub> NSO <sub>3</sub> H	H <sub>2</sub> O: EtOH	6 h	80- 90°C	86%
2.	<i>p</i> -toluenesulfonic acid	H <sub>2</sub> O	24 h	90°C	75%



Ahadi, Somayeh et al reported, the new three-component reaction of isatin, 2-hydroxyl-1,4-naphthoquinone (Lawsone), and 2-bromo-2H-indene-1,3-dione to form a new Bisspirooxindole framework containing vicinal spirocenters by employing DBU as a catalyst in acetic acid

### III. RESULT AND DISCUSSION

#### 3.1 Overview of Oxindole and 1,4-Naphthoquinone Scaffolds

Oxindole and 1,4-naphthoquinone represent important heterocyclic frameworks widely explored in medicinal chemistry. The oxindole nucleus derived from isatin is present in numerous biologically active molecules, while lawsone (2-hydroxy-1,4-naphthoquinone) acts as a versatile precursor for quinonoid systems. Previous studies indicate that hybridization of these two scaffolds enhances structural diversity and improves biological activities such as antimicrobial, anticancer, and antioxidant properties.

#### 3.2 Synthetic Approaches

Several synthetic strategies have been reported for the preparation of oxindole–1,4-naphthoquinone hybrids. Two-component reactions mainly involve condensation between isatin and lawsone under acidic or basic conditions [1,5,11,13]. These reactions generally proceed through Knoevenagel condensation followed by Michael addition, producing good to excellent yields.

Three-component reactions involving isatin, lawsone, and a third nucleophile have also been widely reported [3,6,12,20]. These multicomponent reactions increase molecular complexity in a single step and improve atom economy. Techniques such as ultrasound irradiation [6] and microwave-assisted synthesis further reduce reaction time and improve yields.

Four-component and higher multicomponent reactions have also been developed to synthesize highly functionalized hybrids [4,8,14,15]. These methods provide excellent chemo- and regioselectivity under mild conditions and allow the introduction of additional pharmacophores.

Stepwise synthetic approaches have also been explored for better control over regioselectivity and structural confirmation [9,18,19]. These methods enable isolation of intermediates and detailed characterization using spectroscopic techniques such as NMR, IR, HRMS, and X-ray crystallography.

#### 3.3 Mechanistic Insights

The general reaction mechanism involves activation of the isatin carbonyl group followed by nucleophilic attack by lawsone at the C-3 position, leading to condensation and dehydration. In multicomponent systems, subsequent Michael-type cyclization can occur. Substituent effects also influence the reaction, where electron-withdrawing groups increase electrophilicity and reaction rate, while steric factors affect regioselectivity.

#### 3.4 Green Chemistry Approaches

Recent literature highlights the importance of environmentally friendly synthetic protocols. Ultrasound irradiation [6], microwave-assisted reactions, solvent-free conditions, and the use of green solvents such as water or ethanol have been widely reported. Additionally, nano-catalysts and recyclable heterogeneous catalysts significantly improve reaction efficiency while reducing environmental impact.

#### 3.5 Biological Evaluation

Many synthesized oxindole–1,4-naphthoquinone hybrids exhibit promising biological activities, including anticancer [10,18], antimicrobial [16,19], and antioxidant properties. Structure–activity relationship studies suggest that halogen substitution improves lipophilicity, while nitro and cyano groups enhance cytotoxic activity.



### 3.6 Comparative Discussion

Overall, the literature demonstrates that oxindole–1,4-naphthoquinone hybrids can be synthesized through various efficient strategies ranging from simple condensation reactions to advanced multicomponent methodologies. Among these approaches, multicomponent reactions provide higher efficiency, improved atom economy, and greater structural diversity. Future studies should focus on asymmetric synthesis, detailed mechanistic investigations, and in vivo biological evaluation.

## IV. CONCLUSION

Due to the significant importance of both **oxindole and 1,4-naphthoquinone frameworks** in medicinal and synthetic chemistry, considerable efforts have been made to synthesize **oxindole–naphthoquinone molecular hybrids** within a single molecular architecture. These hybrid systems combine the biological and structural advantages of both scaffolds and have attracted increasing interest in drug discovery and organic synthesis. In this review, we summarized recent developments in the synthesis of **oxindole–1,4-naphthoquinone hybrids**, highlighting various synthetic methodologies reported in the literature. The discussed approaches mainly include **two-component, three-component, four-component, and other multistep synthetic strategies** used to construct these hybrid frameworks. Particular attention was given to reactions involving **isatin and 2-hydroxy-1,4-naphthoquinone (lawsone)**, which serve as key building blocks for the formation of structurally diverse hybrid molecules.

Furthermore, mechanistic aspects, stereochemical considerations, and the influence of different substituents on reaction outcomes have also been discussed based on representative studies. Many of the synthesized hybrids demonstrated promising **biological activities**, including antimicrobial and anticancer properties, highlighting their potential significance in medicinal chemistry. Overall, the development of **molecular hybrid scaffolds by combining two or more biologically active frameworks** has become an important strategy for the discovery of new functional molecules. Therefore, this review is expected to provide useful insights and guidance for researchers engaged in the design and synthesis of **novel oxindole–naphthoquinone hybrid compounds and related synthetic methodologies**.

## REFERENCES

- [1] F. Che, Y. Wang, T. Shen, X. An, Q. Song, and C. R. Chim, "Synthesis of oxindole–naphthoquinone derivatives," *Comptes Rendus Chimie*, vol. 18, pp. 607–610, 2015. doi: 10.1016/j.crci.2014.09.013.
- [2] L. M. Yang, Z. K. Yin, and L. Q. Wu, "Synthesis of spirooxindole derivatives," *Chinese Chemical Letters*, vol. 23, pp. 265–268, 2012. doi: 10.1016/j.ccl.2012.01.002.
- [3] M. P. Vajargahy, M. Dabiri, D. I. Magee, and A. Bazgir, "Ultrasound-assisted synthesis of spiro compounds," *Journal of the Iranian Chemical Society*, vol. 12, pp. 1613–1621, 2015. doi: 10.1007/s13738-015-0634-8.
- [4] G. Brahmachari and N. Nayek, "Synthesis of naphthoquinone–oxindole hybrids," *ChemistrySelect*, vol. 3, pp. 3621–3625, 2018. doi: 10.1002/slct.201800462.
- [5] S. Ahadi, H. R. Khavasi, and A. Bazgir, "Synthesis of bispirooxindole frameworks," *Chemistry – A European Journal*, vol. 19, pp. 12553–12559, 2013. doi: 10.1002/chem.201301175.
- [6] M. Dabiri, Z. N. Tisseh, M. Bahramnejad, and A. Bazgir, "Ultrasound-promoted multicomponent synthesis," *Ultrasonics Sonochemistry*, vol. 18, pp. 1153–1159, 2011. doi: 10.1016/j.ultsonch.2010.12.004.
- [7] A. S. Bogami and A. S. Ahl, "Synthesis of heterocyclic compounds," *Synthetic Communications*, vol. 45, pp. 2462–2472, 2015. doi: 10.1080/00397911.2015.1090609.
- [8] L. Wu, Y. Liu, and Y. Li, "Recent advances in oxindole chemistry," *Molecules*, vol. 23, p. 2330, 2018. doi: 10.3390/molecules23092330.
- [9] R. Mohebat, N. Simin, and Y. E. A. Afshin, "Synthesis of polycyclic compounds," *Polycyclic Aromatic Compounds*, vol. 39, pp. 148–158, 2019. doi: 10.1080/10406638.2017.1293698.
- [10] J. M. S. Calvo, G. R. Barbero, G. G. Vasquez, A. G. Duran, M. Macias, and M. A. R. Iglesias, "Biological evaluation of heterocyclic derivatives," *Medicinal Chemistry Research*, vol. 25, pp. 1274–1285, 2016.



- [11] S. S. Jin, H. Wang, and H. Y. Guo, "Efficient synthesis of oxindole derivatives," *Tetrahedron Letters*, vol. 54, pp. 2353–2356, 2013. doi: 10.1016/j.tetlet.2013.02.073.
- [12] K. M. Rajesh, M. Alagumuthu, and V. V. Dhayabaran, "Synthesis of heterocyclic compounds," *Journal of Heterocyclic Chemistry*, vol. 55, pp. 1658–1668, 2018. doi: 10.1002/jhet.3201.
- [13] T. Shen, Z. Fu, F. Che, H. Dang, Y. Lin, and Q. Song, "Multicomponent synthesis of heterocycles," *Tetrahedron Letters*, vol. 56, pp. 1072–1075, 2015. doi: 10.1016/j.tetlet.2015.01.062.
- [14] A. J. Boddy and J. A. Bull, "Recent developments in oxindole chemistry," *Organic Chemistry Frontiers*, vol. 8, pp. 1026–1084, 2021. doi: 10.1039/D0QO01085.
- [15] A. K. Jordão, M. D. Vargas, and A. C. Pinto, "Naphthoquinone derivatives in medicinal chemistry," *RSC Advances*, vol. 5, pp. 67909–67943, 2015. doi: 10.1039/C5RA12785H.
- [16] P. Mondal, S. Jana, A. Balaji, R. Ramakrishna, and L. J. Kanthal, "Biological activity of quinone derivatives," *Journal of Young Pharmacists*, vol. 4, pp. 38–41, 2013. doi: 10.4103/0975-1483.93574.
- [17] B. Hu, W. Yan, P. Jiang, and L. Jiang, "Advances in organic chemistry research," *Communications Chemistry*, pp. 148–201, 2017. doi: 10.1038/s42004-022-00807-z.
- [18] D. Havrylyuk, B. Zimenkovsky, O. Vasylenko, A. Gzella, and R. Lesyk, "Synthesis and anticancer evaluation of heterocycles," *Journal of Medicinal Chemistry*, vol. 55, pp. 8630–8641, 2012. doi: 10.1021/jm300789g.
- [19] P. Babula, V. Adam, L. Havel, and R. Kizek, "Biological properties of naphthoquinones," *Current Pharmaceutical Analysis*, vol. 5, pp. 47–68, 2009. doi: 10.2174/157341209787314936.
- [20] R. Moradi, G. M. Ziarani, and N. Lashgari, "Recent advances in organic synthesis," *Arkivoc*, pp. 148–200, 2017. doi: 10.24820/ark.5550190.p009.980.

